CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074664

Trade Name : CIMETIDINE HYDROCHLORIDE ORAL SOLUTION

Generic Name: Cimetidine Hydrochloride Oral Solution, 300mg (base)/ 5ml

Sponsor : Hi-Tech Pharmacal Co., Inc.

Approval Date: October 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074664

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074664

APPROVAL LETTER

ANDA 74-664

OCT 28 1997

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

Reference is also made to your amendments dated February 19, April 3, September 19, and October 6, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tagamet Oral Solution, 300 mg/5 mL of SmithKline Beecham Pharmaceuticals).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074664

FINAL PRINTED LABELING

H-T

NDC 50383-050-08

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

CAUTION: Federal law prohibits dispensing without prescription.

8 fl oz (237 mL)

HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

*Each 5 mL (1 teaspoonful) contains:

Cimetidine hydrochloride equivalent to cimetidine	300 mg
Alcohol	2.8%

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 40017-050-08 8

H-T

NDC 50383-050-08

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

CAUTION: Federal law prohibits dispensing without prescription.

8 fl oz (237 mL)

HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

*Each 5 mL (1 teaspoonful) contains:

Cimetidine hydrochloride equivalent to cimetidine	300 mg
Alcohol	2.8%

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 40017-050-08 8

H-T H-T

NDC 50383-050-16

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

*Each 5 mL (1 teaspoonful) contains:

Cimetidine hydrochloride equivalent to cimetidine	300 mg
Alcohol	2.8%

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

7 40017-050-16 1

16 fl oz (473 mL)

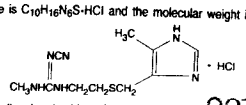
HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION

DESCRIPTION

Cimetidine is a histamine H_2-receptor antagonist. Chemically it is *N*"-cyano-*N*-methyl-*N*'-[2-[[(5-methyl-1*H*-imidazol-4-yl) methyl]thio]-ethyl], guanidine.

The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S$·HCl and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:



Cimetidine contains an imidazole ring, and is chemically related to histamine.

Cimetidine has a bitter taste and characteristic odor.

Solubility Characteristics: Cimetidine hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform and practically insoluble in ether.

Each 5 mL (1 teaspoonful), for oral administration, contains cimetidine hydrochloride equivalent to cimetidine, 300 mg; alcohol, 2.8%. In addition, the oral solution contains the following inactive ingredients: FD&C Yellow No. 6, flavor, hydrochloric acid, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin sodium, sodium chloride, dibasic sodium phosphate anhydrous, sorbitol and water. The pH range is 5.1 to 5.7.

CLINICAL PHARMACOLOGY

Cimetidine competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2 receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) **Acid Secretion:** *Nocturnal:* Cimetidine 800 mg orally at bedtime reduces mean hourly H^+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. Cimetidine 1600 mg orally at bedtime produces 100% inhibition of mean hourly H^+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H^+ activity by 76% for an additional five hours into the following morning. Cimetidine 400 mg b.i.d. and 300 mg q.i.d. decrease nocturnal acid secretion in a dose-related manner, by 47% to 83% over a six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24-Hour Mean H^+ Activity: Cimetidine 800 mg h.s., 400 mg b.i.d. and 300 mg q.i.d. all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg h.s. regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated: Oral cimetidine significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose	Cimetidine	% Inhibition
Betazole	1.5 mg/kg (sc)	300 mg (po)	85% at 2 1/2 hours
Pentagastrin	6 mcg/kg/hr (iv)	100 mg/hr (iv)	60% at 1 hour
Caffeine	5 mg/kg/hr (iv)	300 mg (po)	100% at 1 hour
Insulin	0.03 units/kg/hr (iv)	100 mg/hr (iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45 to 75% and the inhibition of volume ranged from 30 to 65%.

2) **Pepsin:** Oral cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

3) **Intrinsic Factor:** Intrinsic factor secretion was studied with betazole as a stimulant. Oral cimetidine 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying

Cimetidine has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics

Cimetidine is rapidly absorbed after oral administration and peak levels occur in 45 to 90 minutes. The half-life of cimetidine is approximately 2 hours. Both oral and parenteral (I.V. or I.M.) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following I.V. or I.M. administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

Clinical Trials

Duodenal Ulcer

Cimetidine has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer: Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with oral cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates with Various Oral Cimetidine Dosage Regimens*

Regimen	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
week 4	68%	73%	80%	86%
week 6	80%	80%	89%	--
week 8	--	92%	94%	--

* Averages from controlled clinical trials.

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with cimetidine 800 mg h.s., 79 to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of cimetidine has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of 1 year's therapy with cimetidine 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of 1 year with cimetidine 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with cimetidine.

Active Benign Gastric Ulcer

Cimetidine has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with cimetidine 300 mg four times a day or with placebo for 6 weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size. Endoscopically confirmed healing at 6 weeks was seen in significantly* more cimetidine-treated patients than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

* $p < 0.05$

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Cimetidine

2

...trations are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates with Various Oral Cimetidine Dosage Regimens*

Regimen	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
week 4	68%	73%	80%	86%
week 6	80%	80%	89%	--
week 8	--	92%	94%	--

* Averages from controlled clinical trials.

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with cimetidine 800 mg h.s., 79 to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of cimetidine has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of 1 year's therapy with cimetidine 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of 1 year with cimetidine 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with cimetidine.

Active Benign Gastric Ulcer

Cimetidine has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with cimetidine 300 mg four times a day or with placebo for 6 weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size. Endoscopically confirmed healing at 6 weeks was seen in significantly* more cimetidine-treated patients than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

* $p < 0.05$

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Cimetidine	Placebo
total at week 6	63/83 (76%)*	44/80 (55%)

* $p = 0.005$

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with cimetidine than with placebo.

Gastroesophageal Reflux Disease

In two multicenter, double-blind, placebo-controlled studies in patients with gastroesophageal reflux disease (GERD) and endoscopically proven erosions and/or ulcers, cimetidine was significantly more effective than placebo in healing lesions. The endoscopically confirmed healing rates were:

Trial		Cimetidine (800 mg b.i.d.)	Cimetidine (400 mg q.i.d.)	Placebo	p-Value (800 mg b.i.d. vs. placebo)
1	Week 6	45%	52%	26%	0.02
	Week 12	60%	66%	42%	0.02
2	Week 6	50%		20%	<0.01
	Week 12	67%		36%	<0.01

In these trials cimetidine was superior to placebo by most measures in improving symptoms of day- and night-time heartburn, with many of the differences statistically significant. The q.i.d. regimen was generally somewhat better than the b.i.d. regimen where these were compared.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Cimetidine significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of cimetidine was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE

Cimetidine Hydrochloride Oral Solution is indicated in:

(1) Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks (see Dosage and Administration-Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine.

(2) Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer. Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to 5 years.

(3) Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) Erosive gastroesophageal reflux disease (GERD). Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for 12 weeks for healing of lesions and control of symptoms. The use of cimetidine beyond 12 weeks has not been established (see Dosage and Administration-GERD).

(5) The treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

CONTRAINDICATIONS

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

PRECAUTIONS

General: Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of inadequate healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see Adverse Reactions) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses-up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

ADVERSE REACTIONS

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists.

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia that may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions orally of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24-hour period experienced mental deterioration with reversal on Cimetidine discontinuation.

There have been two deaths in adults who have been reported to ingest over 40 grams orally on a single occasion.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see Clinical Pharmacology-Antisecretory Activity-Acid Secretion). This is supported by recent clinical trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime dosage regimen (h.s.).

In a U.S. oral dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions (see Precautions-Drug Interactions) and maximal patient convenience. Patients unhealed at 4 weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with cimetidine 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia that may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions orally of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24-hour period experienced mental deterioration with reversal on Cimetidine discontinuation.

There have been two deaths in adults who have been reported to ingest over 40 grams orally on a single occasion.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see Clinical Pharmacology-Antisecretory Activity-Acid Secretion). This is supported by recent clinical trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime dosage regimen (h.s.).

In a U.S. oral dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions (see Precautions-Drug Interactions) and maximal patient convenience. Patients unhealed at 4 weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with cimetidine 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg h.s., or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (see Clinical Pharmacology-Clinical Trials). 800 mg h.s. is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Erosive Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dosage for the treatment of erosive esophagitis that has been diagnosed by endoscopy is 1600 mg daily in divided doses (800 mg b.i.d. or 400 mg q.i.d.) for 12 weeks. The use of cimetidine beyond 12 weeks has not been established.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Dosage Adjustments for Patients with Impaired Renal Function

Patients with severely impaired renal function have been treated with cimetidine. However, such dosage has been very limited. On the basis of this experience the recommended dosage is 300 mg every 12 hours orally or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

Cimetidine Hydrochloride Oral Solution is a clear yellow, orange flavored solution containing 300 mg of cimetidine per 5 mL (teaspoonful) supplied in 8 fl oz (237 mL) amber PET containers NDC 50383-050-08 and 16 fl oz (473 mL) amber PET containers NDC 50383-050-16.

Store at controlled room temperature, 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

Rev. 5/96
MG #11913

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074664

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.5

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for cimetidine hydrochloride held by SmithKline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Oral Solution

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 1995
Acknowledgment Letter	June 2, 1995
FDA Deficiency Letter	August 4, 1995
Amendment Response	November 27, 1995
FDA Deficiency Letter	April 30, 1996
Amendment Response	June 12, 1996
Amendment Response	September 17, 1996
Amendment Response	February 19, 1997
Amendment Response	April 3, 1997
Amendment Response	Sep 19, 1997

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Oral Solution

14. POTENCY
300 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCL$ Mol. Wt.:288.80

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The originally proposed bulk drug supplier [redacted](b)4 - [redacted] did not have a satisfactory cGMP profile and the inspection by FDA investigators could not be conducted. Therefore, Hi-Tech has proposed an alternate supplier [redacted](b)4 - [redacted] and manufactured an additional exhibit batch using material from the new proposed source. All review comments regarding the data to support the new supplier can be found in this section of the chem review.

The address of the DMF holder is:

[redacted](b)4 - Confidential Business[redacted]

The letter of authorization to reference [redacted](b)4 - [redacted] is provided on p. 9. The status of the DMF and the EES recommendation for the manufacturing plant are acceptable.

The COA for batch #97/001 is on p. 11. The results are within specifications. The firm's own test specifications remain the same. The firm submitted the COAs along with the tests and specifications for each of the excipients used in the additional test batch are on pp. 23-126.

The manufacturing process remains unchanged. The in-process control tests are description, assay (active), assay (parabens), and pH. A copy of the executed batch record begins on p. 142. The bulk solution accountability yield was [redacted](b)4 - Confidential Business[redacted] The in process test results are on p. 168 and they are within the specifications.

The finished product tests and specifications remain the same. The COA for lot 70/050 is on p. 190 and the results are within specifications.

The stability protocol and post approval commitments remain the same. Accelerated stability data for the new test batch packaged in all container configurations begins on p. 204. The results are within specifications.

18. CONCLUSIONS AND RECOMMENDATION
Approvable.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 4/3/97; 10/07/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074664

BIOEQUIVALENCE REVIEW(S)

DIV

ANDA 74-664

NOV 17 1995

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

Reference is made to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cimetidine Hydrochloride Oral Solution 300 mg/5 mL (eq. base).

The following comments pertain only to the bioequivalency issues in the April 28, 1995 submission.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 4 1995

ANDA # 74-664
Cimetidine Hydrochloride
300 mg/5 mL Oral Solution
Reviewer: S.P. Shrivastava
WP #74664W.495

Hi-Tech Pharmacal Co., Inc
Amityville, NY
Submission Date:
April 28, 1995

Review of a Waiver Request

Cimetidine is a H_2 receptor antagonist. It competitively inhibits the action of histamine at the histamine H_2 receptor of parietal cells. It is indicated for the short-term treatments of active duodenal ulcer and active benign gastric ulcer, for maintenance therapy of duodenal ulcer, erosive gastroesophageal reflux disease, and for the treatment of pathological hypersecretory conditions.

Chemically cimetidine is N'-cyano-N-methyl-N'-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]-ethyl]-guanidine, with a molecular weight 252.34. It is soluble in alcohol, slightly soluble in water and insoluble in ether. The hydrochloride salt is soluble in alcohol and water but insoluble in ether.

Cimetidine is rapidly absorbed after oral administration, the peak levels appear in 45-90 minutes. The oral availability of drug is around 62%. Elimination is predominantly by renal route, around 62%. Protein binding is low (19%). The average systemic clearance and half-life is 8.3mL/min/kg and 2.0 hrs., respectively. The drug is widely used in the treatment of ulcers.

The firm is requesting a waiver of bioequivalence study requirements for the test product under 21 CFR 320.22(b)(3). The master formulation of the test product is shown below in comparison with the listed product, Tagamet Oral solution, manufactured by Smithkline Beecham.

The two formulations are qualitativly and quantitatively similar:

1. Since the test product uses cimetidine base as starting material, 0.867% hydrochloric acid is added to obtain a salt solution equivalent to the cimetidine hydrochloride used in the reference drug.

2. The test product contains [redacted](b)4 -[redacted]f sodium phosphate dibasic while the listed product contain[redacted]of sodium phosphate.

   Sodium acid pyrophosphate[redacted](b)4 -[redacted]has been reported to decrease the bioavailability of another H_2 receptor antagonist, ranitidine oral solution, by decreasing the small intestine transit time to 56% [see Pharm. Res. 10(7):1027-30 (1993)]. However, the test product contains less sodium phosphate [redacted](b)4 -[redacted]han does the listed product[redacted](b)4 -[redacted]

3. Propylene glycol [redacted](b)4[redacted]gher than the reference product, it is within the IIG limits.

4. The two products contain different flavors, which are accepted.

5. The ANDA batch size is (b)4 and the proposed production batch size is (b)4

Deficiency Comment

None

Recommendation

The Division of Bioequivalence agrees that the information submitted by Hi-Tech Pharmacal Co., demonstrates that cimetidine hydrochloride oral solution, 300 mg base/5 mL, falls under 21 CFR Section 320.22 (b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test oral solution formulation to be bioequivalent to Tagamet Oral Solution, 300 mg/5 mL, manufactured by Smithkline Beecham.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

/S/ 9/22/95

Concur: /S/ Date: 11/4/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

SPS/sps/9-9-95/74664W.495
cc: ANDA # 74-664 (Original, Duplicate), HFD-600 (DHare), HFD-630, HFC-130 (JAllen), HFD-655 (RNPatnaik, SPShrivastava), Drug File, Division File.